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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/652,493	08/31/2000	Mina J. Bissell	IB-1398	3653

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EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/06/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/652,493	BISSELL ET AL.	
	Examin r	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,22-24,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,22-24,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Misook Yu.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 22-24, 29, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 5 recites "potential tumorigenicity" but it is not clear what the metes and bounds are for the phrase. Neither the specification nor the claims define what is being claimed for patent protection by the phrase.

Claim 1 recites "medium surrounding cells" but it is not clear what the metes and bounds are for the phrase. Claim 4 indicates one example of the phrase is blood. What else is "medium surrounding cells"? The specification does not define what is being claimed for patent protection by the phrase.

Claims 1-8 are confusing, therefore indefinite because it is not clear what is being claimed by instant claims 1-8. Claims 1-8 say they are drawn to a method of measuring potential tumorigenicity by detecting 120-130 kD (a proteolytic fragment) alpha-dystroglycan, wherein the presence of the dystroglycan indicates higher potential tumorigenicity. The claims could be interpreted as drawn to a cancer screening method by detecting the proteolytic fragment. The claims, as written, could be also interpreted as **a research proposal** of assessing if the 120-130 kD alpha dystroglycan fragment could be used as a biomarker for either presence of cancer or antecedent marker for cancer.

For the purpose of this office action, the examiner will assume that the claims are drawn to tumor screening method using the proteolytic fragments of alpha-dystroglycan

as a biomarker since a method of assessing whether the 120-130 kD alpha dystroglycan could be used as a biomarker (the second interpretation above) is just an invitation for further research, i.e., not a substantial, specific or credible utility. However, this treatment does not relieve applicant the burden of responding this rejection.

Claim 22-24, 29, and 30 are confusing and it is not clear what is being claimed for patent protection by the claims. Are they drawn to tumor detection method using the proteolytic fragments of alpha-dystroglycan as a biomarker? See rejection of claims 1-8 above.

Claims 1-8, 22-24, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are interpreted as a method of assessing cancer risk using the proteolytic alpha-dystroglycan fragments. See rejection of claims 1-8 above.

The specification discloses:

1) At Fig. 1, and Examples 1 and 2 (pages 17-20), a smaller fragment (120-130 kDa) of alpha-dystroglycan is detected in the supernatant of SCg6 mammary carcinoma cell line culture and this detection is due to shedding of proteolytic fragment of 180 kDa alpha-distoglycan (normal size) , adding a metaloprotease inhibitor GM6001 to the cell culture reduces this shedding.
2) At Fig. 2, the immunoblot of whole cell extracts show that some cell lines express both alpha- and beta dystroglycan for example BT474, lane 2, and other cell lines express only beta-dystroglycan for example, MCF-7.
3) At Fig. 3, and Example 3 (page 20-23), adding the metalprotease inhibitor restores the tumor phentype of several tumor cell lines.
4) At Example 5 (pages 24 and 25) restoration of dystroglycan function to the tumoriogenic cell line HMT-3522-T4 by transfection of DNA

overexpressing a human dystroglycan restored normal phenotype of the cell line.

One cannot extrapolate the teachings of the specification to the claimed invention because the specification provides neither guidance on nor exemplification of how to correlate the data presented in the specification with the ability to use alpha-dystroglycan fragments for the assessment of cancer risk. It is not clear whether the 120-130 kD or the 60 kD fragment is circulating in the blood or the fragment is further degraded into smaller fragmen by many proteolytic enzymes present in vivo. Further, it is not clear whether the antibody disclosed in the instant application could be used to detect the fragment(s) circulating in blood if the fragments are further degraded. The specification does not teach if some normal cells in vivo secrete the fragments for yet unknown functions. For example, Wirth et al (Eur Urol 1993;24 Suppl 2:6-12, Abstract only) teach that the well known blood circulating prostate tumor maker (i.e. PSA) by shedding of prostate membrane antigen is detected in normal blood: PSA concentration in blood is relevant as cancer marker, not just presence or absence of it. Further, the specification does not teach what kinds of tumor growth could be correlated with the detection of the fragments in blood. In short, the specification does not present any in vivo data to correlate either detection of the fragment in blood or absence of the fragment on cell surface to growth of any tumor. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to instant invention. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of tumorigenicity have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome.

The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). As the summary of the specification above indicates the specification does not teach if the proteolytic fragment could be used as a biomarker for potential tumorigenicity odetected in blood or any other in vivo medium surrounding the cells.

Further, one cannot extrapolate the teaching of the specification to the claimed invention because the specification does not teach that method of positively correlating tumor cell growth *in vivo* to either detection of the smaller fragment shedding into blood, or to absence of the smaller fragment on cell surface. The *in vitro* demonstration of restoring normal phenotype of cancer cells with the protease inhibitor or with overexpression of human dystroglycan cannot be correlated to the invention as claimed, because the characteristics of cultured cell lines generally differ significantly from the characteristics of in vivo primary cancers or metastatic cancers. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994,

12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that the proteolytic fragments could be detected in blood or cell surface *in vivo*.

The specification provides insufficient guidance, and provides no working examples of correlating in vivo tumor growth to either detection of 120-130 kDa (or 60 kDa) fragments of alpha-dystroglycan or to absence of the fragment on cell surface, which would provide guidance to one skilled in the art to use the claimed invention without undue experimentation. Considering lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the claimed invention.

Claim 22-24, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amended claims are drawn to assay method of positively correlating detection of alpha-dystroglycan fragments in blood to tumor cell growth. This examiner is unable to find support for this positive correlation assay method in the originally filed specification. Applicant is requested to point support for the amendment.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
November 3, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800, 600